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Comparison of Manual and Semiautomatic Volume of Interest Drawing For the Analysis of Spinal Cord Myelin Pet Imaging

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Abstract **-** This study aims to compare the manual and semiautomatic method for volume of interest (VOI) drawing of Positron Emission Tomography (PET) images with Carbon-11 labeled Pittsburgh Compound B ([^{11}C]PIB) of Cervical Spinal Cord (SC). Studies using PET images of spinal cord are scarce, probably, due to the difficulty associated with reduced dimensions and respiratory movement of this region, therefore, more suitable method of drawing the VOIs in this region still needs further evaluation. [^{11}C]PIB PET images and T1-weighted MRI were acquired from 10 healthy volunteers in a simultaneous hybrid PET/MR system. The VOIs were placed using: 1) manually, using iso-contour tool, and 2) semi-automatically, using ellipse and rectangle shape tool, slice by slice, oriented by vertebral levels (C1/C2-C4) and drawing in the axial and sagittal plane. The statistical analyses were performed by GraphPad Prism 8 software, using one way ANOVA. The results are presented in SUV (Standardized Uptake Value) at C1/C2, C3 and C4 levels. There were no statistical differences between the four VOI drawing strategies. Manual and semi-automatic drawing showed similar results, allowing the choice by a personal analyst preference.

Keywords: [^{11}C]PIB PET, Spinal Cord, VOI-drawing, PET/MRI.

1. Introduction

Studies using Positron Emission Tomography (PET) images of Spinal cord are scarce, probably due to spinal cord small dimensions and voluntary and involuntary movement (swallowing, cardiorespiratory movement) of this region[1], which could lead to image artefacts. While multiple software for analysis of brain is established and validated[1]–[3], the same does not occur for the spinal cord[4]–[6].

The low spatial resolution of PET images makes the definition of spinal cord complex, however, equipment associated with magnetic resonance imaging (PET/MR) may assist in reducing this difficulty[2]–[4].

The radiopharmaceutical N-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, or [^{11}C]PIB, also called Pittsburgh Compound B, is a radiopharmaceutical used for the detection of β-amyloid plaques[10], and has also been shown to be a marker of white matter damage of neurodegenerative diseases such Multiple Sclerosis[11]. Like [^{11}C]PIB, all β-amyloid tracers bind to white matter regardless the presence of amyloid beta plaque[12].

The study of spinal cord has great importance to evaluate neurodegenerative process and requires an appropriate method of drawing the Volumes of Interest (VOIs) for quantification of PET images. More precise evaluation of spinal cord images can help for new insights in spinal cord diseases. Based on this considerations, this study aim to compare the manual and semiautomatic methods of drawing volume of interest (VOI) on axial and sagittal planes images of 10 healthy volunteers, using Positron Emission Tomography (PET) images with Carbon-11 labeled Pittsburgh Compound B ([^{11}C]PIB) of Cervical Spinal Cord (SC).

2. Materials and methods

2.1. Participants

This study was approved by the Ethics Committee of the University of São Paulo Medical School (CAPPesq: 4.596.501), conducted according to the Declaration of Helsinki and Norms of Research involving Human Beings (Res. CNS 196/96) of the National Health Council[13].

The [^{11}C]PIB PET images of 10 healthy volunteers were evaluated, consisting of 7 females and 3 males, with mean age of 36.3 years (SD ±14.23). The inclusion and exclusion criteria are reported previously[14].

The images were acquired in a hybrid PET/MR 3 Tesla system (SIGNA, General Electric) in the Center of Nuclear Medicine of the Hospital das Clínicas of the University of São Paulo Medical School (HC-FMUSP). The radiotracer [^{11}C]PIB was produced in house, and injected intravenously (185–370 MBq).

PET images were reconstructed using the 3D Ordered Subset Expectation Maximization algorithm (OSEM) with two interactions and 28 subsets, using point scattering function and 3 mm Gaussian spatial filter (Z-axis), with 21 timeframes (6×10 seconds, 2×30 seconds, 3×1 minutes, 2×2 minutes, 2×3 minutes, 3×5 minutes, 3×10 minutes) totalizing 60 minutes of dynamic acquisition. The T1-weighted MRI was acquired using a Head Neck Unit coil (HNU).

3.2. Volume of Interest (VOI) drawing

The images used in this study were anonymized before any analysis, preserving the privacy of the research participants. Initially, due to the spinal cord region suffer the influence of movement artifacts, the [^{11}C]PIB PET dynamic images (0-60 minutes) were corrected for movement.

Motion correction was applied to the 21 timeframes using as reference the 11 initial frames (as they are very short), interpolation method with 2 pixels rate, Gaussian smoothing of 6 millimeters, and it was saved as NIfTI format.

The dynamic [^{11}C]PIB PET image (0-60 minutes) with motion correction was fused with T1-weighted MRI of each subject. The T1-weighted MRI and PET images were fused as illustrated in **Figure 1.** The images fusion and volumes of interest (VOIs) drawing were performed on PMOD 4.1 software.

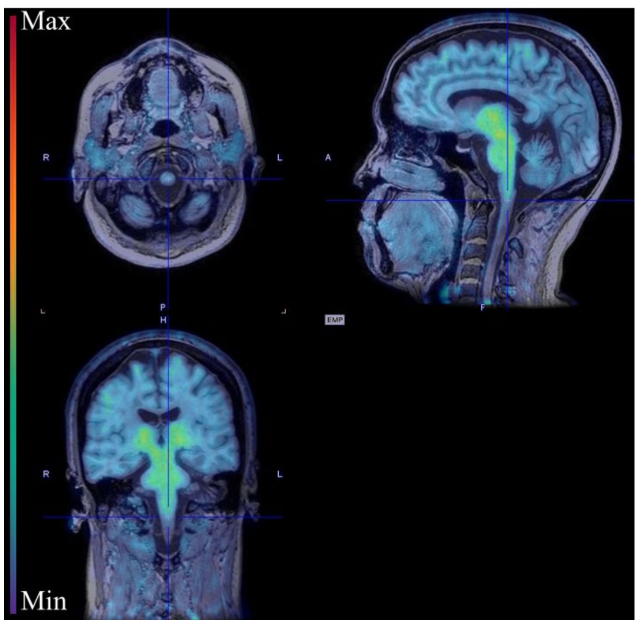

Figure 1. PET image showing timeframe 20 (40-50 minutes), fused with T1-weighted MRI.

Once the image was fused, the VOI drawing strategies were performed on spinal cord at the C1/C2, C3 and C4 vertebrae levels. Manual (iso-contour tool with point-to-point drawing) and semiautomatic forms (ellipse and rectangle drawing tool) were used. The VOI drawing was performed on axial and sagittal plans, slice by slice, to obtain the final spinal cord VOIs at each vertebrae level. The different types of drawing are illustrated in **Figure 2.**

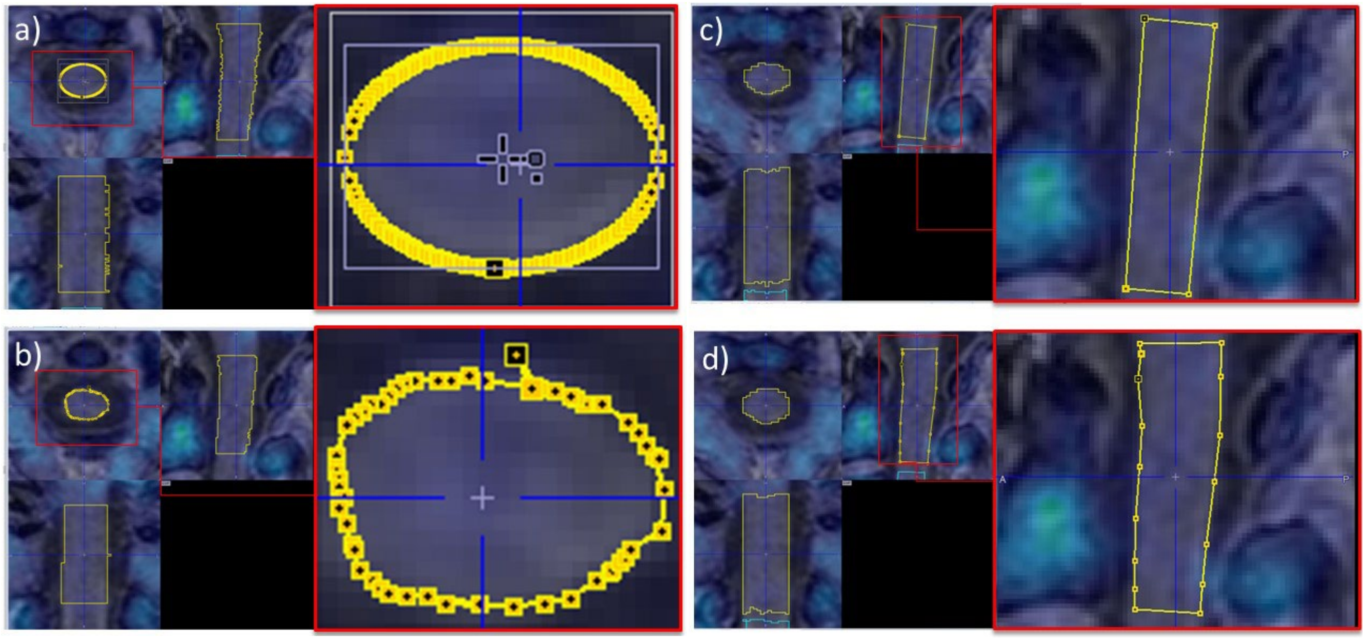

Figure 2. Illustrative images of VOIs drawing semiautomatic tool: a) with ellipse shapes in axial plane; b) manual iso-contour tool in the axial plane; c) semiautomatic tool, with rectangle shape in sagittal plane; and d) manual iso-contour tool at sagittal plane.

The VOIs on spinal cord were oriented by the vertebrae level, being C1 and C2 evaluated together due to the anatomic merged morphology. The superior limit was based on odontoid process of C1/C2, avoiding the brainstem region. The inferior limit of C4 VOIs was based on the vertebrae, avoiding the edge of MRI and PET images. The drawing was executed on T1-Wheighted MRI based on timeframe 20 of the PET image, minimizing movement artifacts, as illustrated in **Figure 3.**

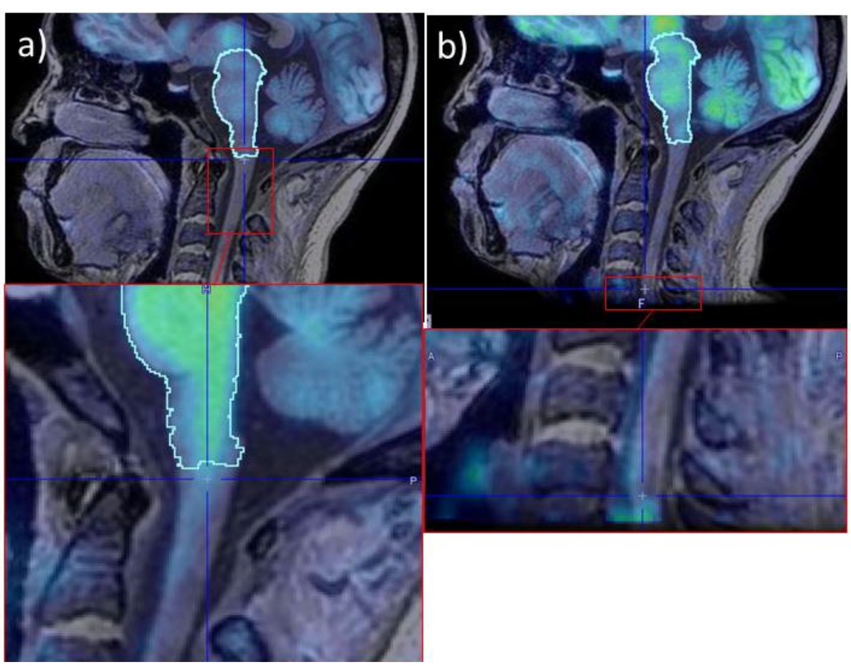

Figure 3. Superior limits of VOIs on spinal cord at; a) C1/C2 level, based on the odontoid process (white arrow) and the brainstem region (light blue drawing); and b) inferior limits at C4 level.

3.3. PET Image Quantification

The [11C]PIB uptake quantification was expressed as Standardized Uptake Value (SUV) of the last 20 minutes (40-minutes), calculated by equation (1)[15].

$$\mathrm{SUV} = \frac{Ac}{D * W} \tag{1}$$

Ac= Radioactivity Concentration (MBq/ml)
D= injected radioactivity (MBq)
W=body weight (g)

The variability of each VOI drawing strategy was measured by coefficient of variation (CV), calculated by equation (2) [16]–[18].

$$CV = \frac{\sigma}{\mu} \tag{2}$$

σ= Standard deviation
μ=mean

2.4. Statistical analyses

The data quantification was obtained by PMOD 4.1 software. Normality was evaluated by Shapiro Wilk test. One-way ANOVA followed by the Tukey's post-test was applied for normal data. Nonparametric test (Kruskal Wallis test, followed by Dunn's post-test) was applied for the data that did not pass on the normality test.

The variables considered for the analysis were the mean uptake of the last 20 min (40-60 minutes) and the coefficient of variation of this data.

Each VOI was evaluated separately. The p-value < 0.05 was considered significant. The graphic data are expressed as mean ± standard deviation of the mean (SD). For data analysis and graph construction, the GraphPad Prism 8 software was used.

3.Results

The [11C]PIB uptake of 10 healthy volunteers obtained by the different VOI drawing strategies were quite similar, meaning that the drawing method do not interfere in the results, as illustrated in **Figure 4**.

The coefficient of variation also showed similar variability in the four drawing strategies, being the descriptive data presented on **Table 1** and **Figure 5.**

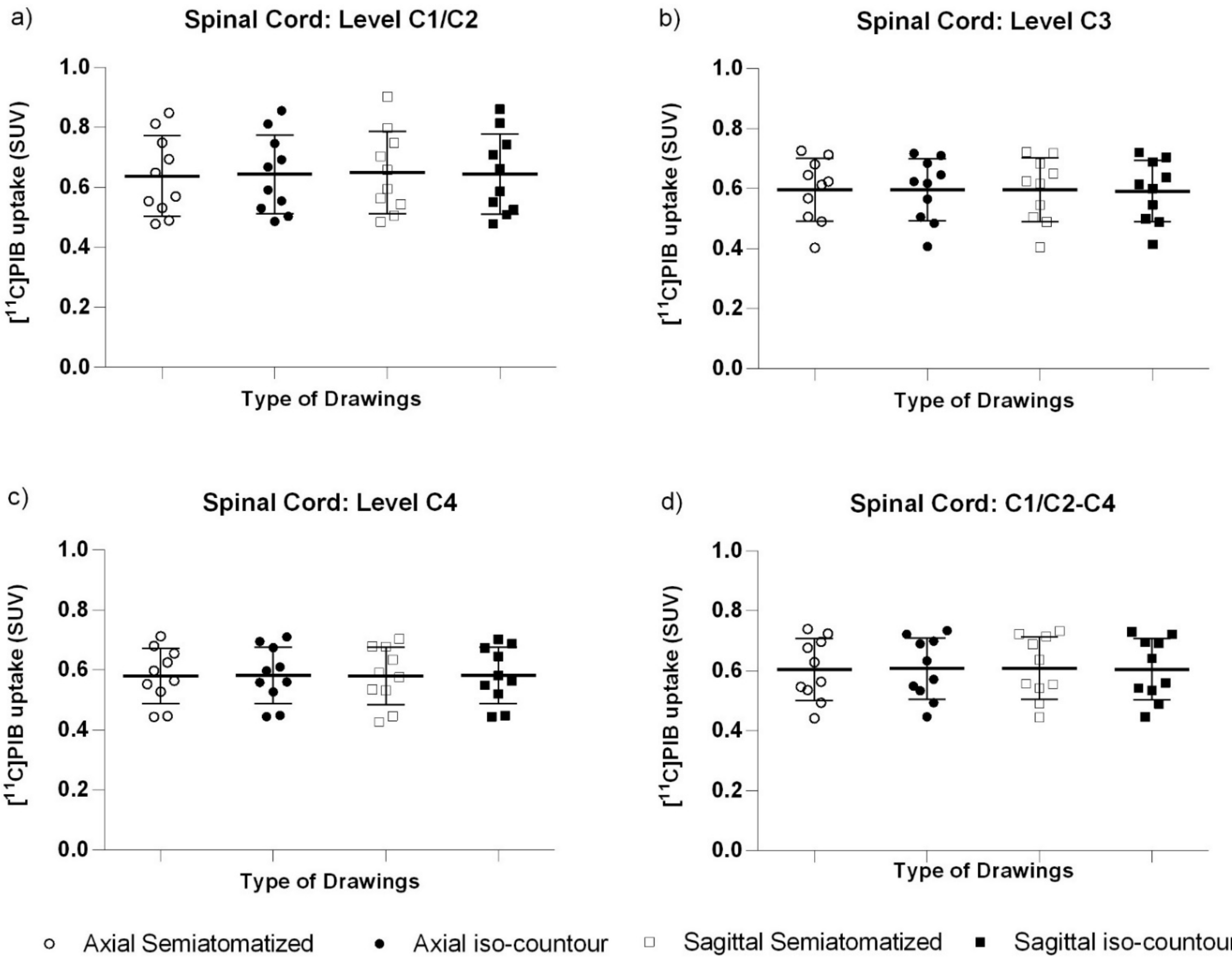

Figure 4- [11C]PIB uptake (SUV) in VOIs drawn manually and semiautomatically on spinal cord of healthy volunteers along all levels: a) C1/C2-C4; b) C1/C2; c) C3; and d) C4

Table 1- Descriptive data

Spinal cord	**C1-C4**				**C1/C2**				**C3**				**C4**			
VOI	AS	AI	SS	SI	AS	AI	SS	SI	AS	AI	SS	SI	AS	AI	SS	SI
Mean	0,60	0,60	0,60	0,60	0,64	0,60	0,70	0,60	0,60	0,60	0,60	0,60	0,60	0,60	0,60	0,60
(SD)	0,10	0,10	0,10	0,10	0,13	0,10	0,10	0,10	0,10	0,10	0,10	0,10	0,10	0,10	0,10	0,10
Coefficient of Variation	0,20	0,20	0,20	0,20	0,21	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,20

AS: Axial semiautomatic; **AI**: Axial iso-contour; **SS**: Sagittal semiautomatic; **SI**: Sagittal iso-contour; **SD**: Standard Deviation.

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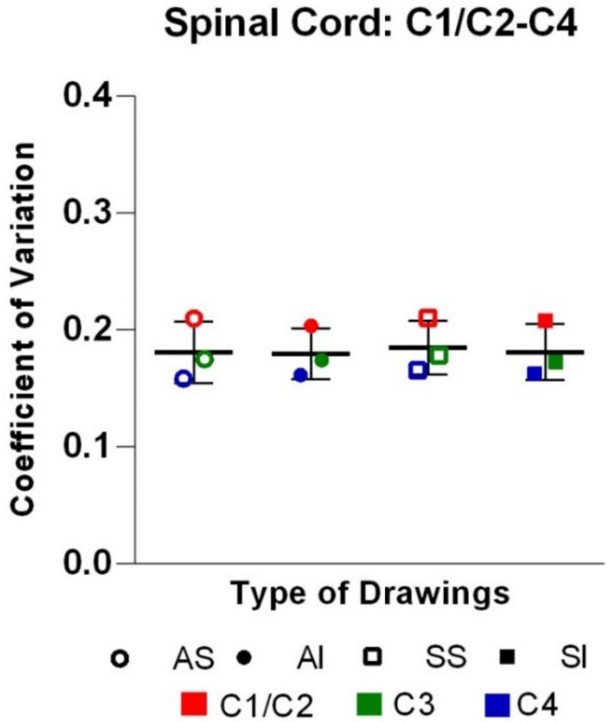

Figure 5-Coefficient of variation of [^{11}C]PIB (SUV) in VOIs drawn manually and semiautomatically on spinal cord at C1/C2, C3 and C4 levels. **AS**: Axial semiautomatic; **AI**: Axial iso-contour; **SS**: Sagittal semiautomatic; **SI**: Sagittal iso-contour; **SD**: Standard Deviation.

4. Discussion

This study presented the comparison of manual and semiautomatic drawing methods for the analysis of spinal cord in [^{11}C]PIB PET images of 10 healthy volunteers.

Spinal cord drawings can be organized into manual, semiautomatic, or fully automatic methods. One study comparing fully automatic and semiautomatic methods showed significant differences on results analyzing the same individual[19]. On the other hand, one study using manual and semi-automatic drawings methods on spinal cord demonstrates non-significant differences between them[20].

Our study found no significant differences between manual vs semiautomatic drawings of the human spinal cord. This were the same results found by Mendili et al., who evaluated semiautomatic and manual methods in the axial plane, performed by operators with and without experience in spinal cord drawing, using MRI of 111 healthy individuals with involvement of spinal cord[21].We did not found studies evaluating these methods performed on sagittal plane.

It is worth to mention that the drawings differed greatly in time-consuming. Drawings on axial planes are more time-consuming compared to drawings on sagittal plane. The iso-contour drawing spends 4 hours to be executed on axial plane, and 1 hour on sagittal plane, whereas semiautomatic drawings spend 1 hour to be executing on axial plane, and 30 minutes on sagittal plane.

A low variability was obtained at all evaluated spinal cord drawings strategies (Coefficient of variation of 0.2). Our results had less variability than showed by Mendilli et al (Coefficient of variation inter and intragroup of 1.3 and 0.6, respectively). This higher variability can be explained by the two operator (one without experience), and the number of individuals analyzed (n=111).

This study has the limitation of analyzing only 10 healthy volunteers, being necessary also to be performed in spinal cord in pathological conditions for testing if the results are the same. In addition, the [^{11}C]PIB PET images were acquired focusing in brain analysis[14], [22], therefore the field of view (FOV) of the equipment restricted the analysis of the cervical cord at level C4.

As this study showed four VOIs drawings with similar results, the time-consuming and analyst preference would be the factors for the strategy choice, although future studies in pathological spinal cord are recommended, as, for example, spinal cord of patients with multiple sclerosis, disease which lesions and atrophy on spinal cord are present on almost 90% of the patients[23], [24], correlating with a worst prognostic and debility[25], [26].

5. Conclusion

Comparing the four VOI drawing strategies, in axial and sagittal plane using semiautomatic and manual methods, there were no statistical differences of [^{11}C]PIB uptake among them. Therefore, is possible to conclude that the manual and semiautomatic VOI drawings have similar results, allowing the choice based on the analyst preference, however, the semiautomatic drawings are more time-effective, what would make this method more suitable for analyzing a bigger sample size data.

6. Acknowledgements

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7. References

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